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L25	L24 and l15	1	L25
L24	l1 and l2 and l14	143	L24
L23	l1 and l2 and l12 and l14	0	L23
L22	l12 and l1	17	L22
L21	l12 and l1 and l14	0	L21
L20	l1 and l19	0	L20
L19	l18 and l14	2	L19
L18	L12 and l2	86	L18
L17	l12 and l15	1	L17
L16	l15 and l14	2	L16
L15	l4 same l2	1662	L15
L14	tablet.ti. or tablet.ab.	3921	L14
L13	l12 and l9 and l1 and l2	7	L13
L12	gabapentin	143	L12
L11	l10 and ((424/451 |424/464 |424/474)!.CCLS.)	1	L11
L10	l9 and l8	301	L10
L9	tablet or capsule	116680	L9
L8	l6 and l2 and l1	328	L8
L7	l6 same l2 same l1	0	L7
L6	l5.ti. or l5.ab.	9936	L6
L5	(amino adj1 acid) or (cyclic adj1 amino adj1 acid) or (amino acid)	84617	L5
L4	stabilizer?	78322	L4
L3	adjuvant? or excipient?	62687	L3
L2	ethanol	204258	L2
L1	corn starch	21920	L1

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L16: Entry 1 of 2 File: USPT

DOCUMENT-IDENTIFIER: US 6174873 B1
TITLE: Oral administration of adenosine analogs

Abstract Text (1):
Disclosed are compositions including an adenosine analog, wherein the composition comprises a dosage form suitable for oral (co)administration. Also disclosed are compositions including adenosine analogs, wherein the composition is in a dosage form including a pill, capsule, lozenge, or tablet, and compositions including adenosine analogs, wherein the composition is in a dosage form comprising a liquid. Additionally disclosed are methods of administering the inventive composition, and kits including the inventive compositions.

Brief Summary Text (82):
In the case of drinkable solutions the following substances may be used as stabilizers or solubilizers: lower aliphatic mono- and multivalent alcohols with 2-4 carbon atoms, such as ethanol, npropanol, glycerol, polyethylene glycols with molecular weights between 200-600 (for example 1 to 40% aqueous solution), diethylene glycol monoethyl ether, 1,2-propylene glycol, organic amides, for example amides of aliphatic C.sub.1 -C.sub.6 -carboxylic acids with ammonia or primary, secondary or tertiary C.sub.1 -C.sub.4 -amines or C.sub.1 -C.sub.4 -hydroxy amines such as urea, urethane, acetamide, N-methyl acetamide, N, N-diethyl acetamide, N, N-dimethyl acetamide, lower aliphatic amines and diamines with 2-6 carbon atoms, such as ethylene diamine, hydroxyethyl theophylline, tromethamine (for example as 0.1 to 20% aqueous solution), aliphatic amino acids.

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L16: Entry 2 of 2 File: USPT

DOCUMENT-IDENTIFIER: US 5827652 A
TITLE: Zeaxanthin formulations for human ingestion

Abstract Text (1):
Preparations are disclosed containing the 3R-3'R stereoisomer of zeaxanthin as a sole detectable isomer, packaged for oral ingestion by humans as a therapeutic drug or nutritional supplement. Zeaxanthin is a yellow carotenoid pigment found in the macula (in the center of the human retina), which helps protect retinal cells against phototoxic damage. The pure R-R stereoisomer can be prepared by fermenting cells, such as Flavobacterium multivorum (ATCC 55238), which do not create any detectable quantity of the undesired and potentially toxic S-S or S-R isomers, and which do not synthesize any other carotenoids. The R-R isomer can be concentrated, in large quantities and at low cost, into a viscous oily fluid containing about 5 to 20% zeaxanthin, by means of a simple solvent extraction process. This oily fluid can be mixed with a carrier such as vegetable oil and enclosed within a digestible capsule, comparable to a conventional capsule containing Vitamin E. Alternately, a zeaxanthin fluid can be added to various types of foods, such as margarine, dairy products, syrup, cookie dough, and certain types of meat preparations which are not subjected to harsh cooking. Additional purification steps can also be used to purify zeaxanthin to a granular or powdered state which contains nearly pure zeaxanthin. Such processing can be used to create formulations such as ingestible tablets, and particulate formulations that can be added to soups, salads, drinks, or other foods. Preferred stabilizers and anti-oxidants are also disclosed herein. When consumed by humans in any of these modes, the purified R-R stereoisomer of zeaxanthin can help treat and prevent macular degeneration, one of the leading causes of blindness and vision loss, especially among the elderly.

Detailed Description Text (53):
Various candidate stabilizers have been tested by the Applicants. The best results obtained to date have used a combination of stabilizing agents, which are mixed together in a small quantity of a suitable solvent (such as about 2 milliliters of ethanol for a 20 liter fermentation vessel) before being added to the cells. The preferred stabilizer mixture contains tertiary butyl hydroquinone (abbreviated as TBHQ; also called 2-(1,1-dimethyl)-1,4-benzenediol) at a quantity which will generate a final concentration ranging from about 250 .mu.g/L up to about 50 mg/L after being mixed with the cells; ethoxyquin at a post-mixing concentration ranging from about 250 .mu.g/L to about 250 .mu.g/L; .alpha.-tocopherol at a concentration ranging from about 250 .mu.g/L to about 250 mg/L; and EDTA (ethylene diamine tetra acetic acid) at a concentration ranging from about 500 .mu.g/L to about 500 mg/L. Suitable concentrations can vary widely, and will depend on various factors such as subsequent purification steps and the intended mode of packaging and ingestion. Preferred concentrations for single-pass THF extraction followed by mixing with vegetable oil and watertight encapsulation in a vitamin-type pill are about 25 to 50 mg/L for TBHQ; 250 to 500 .mu.g/L for ethoxyquin, 250 to 500 .mu.g/L for .alpha.-tocopherol; and 500 to 1000 .mu.g/L for EDTA.

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L25: Entry 1 of 1 File: USPT

DOCUMENT-IDENTIFIER: US 6174873 B1
TITLE: Oral administration of adenosine analogs

Abstract Text (1):
Disclosed are compositions including an adenosine analog, wherein the composition comprises a dosage form suitable for oral (co)administration. Also disclosed are compositions including adenosine analogs, wherein the composition is in a dosage form including a pill, capsule, lozenge, or tablet, and compositions including adenosine analogs, wherein the composition is in a dosage form comprising a liquid. Additionally disclosed are methods of administering the inventive composition, and kits including the inventive compositions.

Brief Summary Text (78):
Furthermore, the adenosine analogs may be administered or coadministered with conventional pharmaceutical excipients and additives. These include, but are not limited to, gelatin, natural sugars such as raw sugar or lactose, lecithin, pectin, starches (for example corn starch or amylose), dextran, polyvinyl pyrrolidone, polyvinyl acetate, gum arabic, alginic acid, tylose, talcum, lycopodium, silica gel (for example colloidal), cellulose, cellulose derivatives (for example cellulose ethers in which the cellulose hydroxy groups are partially etherified with lower saturated aliphatic alcohols and/or lower saturated, aliphatic oxyalcohols, for example methyl oxypropyl cellulose, methyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose phthalate), fatty acids as well as magnesium, calcium or aluminum salts of fatty acids with 12 to 22 carbon atoms, in particular saturated (for example stearates), emulsifiers, oils and fats, in particular vegetable (for example, peanut oil, castor oil, olive oil, sesame oil, cottonseed oil, corn oil, wheat germ oil, sunflower seed oil, cod liver oil, in each case also optionally hydrated); glycerol esters and polyglycerol esters of saturated fatty acids C.sub.12 H.sub.24 O.sub.2 to C.sub.18 H.sub.36 O.sub.2 and their mixtures, it being possible for the glycerol hydroxy groups to be totally or also only partly esterified (for example mono-, di- and triglycerides); pharmaceutically acceptable mono- or multivalent alcohols and polyglycols such as polyethylene glycol and derivatives thereof, esters of aliphatic saturated or unsaturated fafty acids (2 to 22 carbon atoms, in particular 10-18 carbon atoms) with monovalent aliphatic alcohols (1 to 20 carbon atoms) or multivalent alcohols such as glycols, glycerol, diethylene glycol, pentacrythritol, sorbitol, mannitol and the like, which may optionally also be etherified, esters of citric acid with primary alcohols, acetic acid, urea, benzyl benzoate, dioxolanes, glyceroformals, tetrahydrofurfuryl alcohol, polyglycol ethers with C.sub.1 -C.sub.12 -alcohols, dimethylacetamide, lactamides, lactates, ethylcarbonates, silicones (in particular medium-viscous polydimethyl siloxanes), calcium carbonate, sodium carbonate, calcium phosphate, sodium phosphate, magnesium carbonate and the like.

Brief Summary Text (81):
As mentioned above, the adenosine analogs may be orally administered or coadministered in a liquid dosage form. For the preparation of solutions or suspensions it is, for example, possible to use water, particularly sterile water, or physiologically acceptable organic solvents, such as alcohols (ethanol, propanol, isopropanol, 1,2-propylene glycol, polyglycols and their derivatives, fatty alcohols, partial esters of glycerol), oils (for example peanut oil, olive oil, sesame oil, almond oil, sunflower oil, soya bean oil, castor oil, bovine hoof oil), paraffins, dimethyl

sulphoxide, triglycerides and the like.

Brief Summary Text (82):
In the case of drinkable solutions the following substances may be used as stabilizers or solubilizers: lower aliphatic mono- and multivalent alcohols with 2-4 carbon atoms, such as ethanol, npropanol, glycerol, polyethylene glycols with molecular weights between 200-600 (for example 1 to 40% aqueous solution), diethylene glycol monoethyl ether, 1,2-propylene glycol, organic amides, for example amides of aliphatic C.sub.1 -C.sub.6 -carboxylic acids with ammonia or primary, secondary or tertiary C.sub.1 -C.sub.4 -amines or C.sub.1 -C.sub.4 -hydroxy amines such as urea, urethane, acetamide, N-methyl acetamide, N, N-diethyl acetamide, N, N-dimethyl acetamide, lower aliphatic amines and diamines with 2-6 carbon atoms, such as ethylene diamine, hydroxyethyl theophylline, tromethamine (for example as 0.1 to 20% aqueous solution), aliphatic amino acids.

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L17: Entry 1 of 1 File: USPT

DOCUMENT-IDENTIFIER: US 6350768 B1
TITLE: Combination of riluzole and of gabapentin and its use as a medicament

Abstract Text (1):
The present invention relates to the combination of riluzole and of gabapentin or one of their pharmaceutically acceptable salts and its use as a medicament which is useful in particular for the prevention and/or treatment of motoneuron diseases.

Brief Summary Text (2):
The present invention relates to the combination of riluzole and of gabapentin or one of their pharmaceutically acceptable salts and its use as a medicament which is useful in particular for the prevention and/or treatment of motoneuron diseases.

Brief Summary Text (6):
Gabapentin has also been recommended for the treatment of neurodegenerative diseases and in particular of amyotrophic lateral sclerosis U.S. Pat. No. 5,084,479). Gabapentin is currently marketed under the name NEURONTIN.RTM. for the treatment of epilepsy.

Detailed Description Text (2):
It has now been found that the combination of riluzole and of gabapentin or one of their pharmaceutically acceptable salts makes it possible to increase the survival of the motoneurons more considerably than riluzole alone or gabapentin alone.

Detailed Description Text (4):
Purified motoneurons prepared from the spinal cord of rat embryos at 14 days of gestation are cultured in the presence of optimum concentrations of recombinant "brain-derived neurotrophic factor" (BDNF), one of the principal neurotrophic factors for the survival of the motoneurons. 22 hours later, riluzole and gabapentin are added to the motoneurons either alone or in combination. After a further 2 hours, dilutions of dialyzed sera from patients suffering from ALS are added. On the next day, the number of surviving motoneurons is evaluated by direct counting under a phase contrast microscope.

Detailed Description Text (8):
The stock solution of gabapentin is prepared directly by dissolving 17.1 mg of gabapentin in 1 ml of double distilled water.

Detailed Description Text (15):
The purified motoneurons are inoculated at a density of 1000 motoneurons per well into 16-mm wells previously coated with polyornithine-laminin. The culture medium is the Neurobasal medium supplemented with complement B27 (Life Technologies) and 2% of horse serum but with no antibiotic, the total volume being 0.5 ml. The motoneurons are inoculated in the presence of neurotrophic factor BDNF (1 ng/ml; Sigma) and left in sedimentation for 22 hours during which they attach to the support and develop neurites. Riluzole (3.times.10.sup.5 M) and gabapentin (3.times.10.sup.-5 M) are added either separately or as a combination in a series of 4 wells. Two hours later, a dialyzed serum from patients suffering from ALS is added to the wells. The motoneurons are then cultured for 1 day at 37.2.degree. C. before evaluating their survival.

Detailed Description Text (25):

c--when the medium is treated with gabapentin alone, the survival of the motoneurons is 8%

Detailed Description Text (26):
d--when the medium is treated with the combination of riluzole and of gabapentin, the survival of the motoneurons is 61%, thus demonstrating a synergy between the two molecules.

Detailed Description Text (28):
Gabapentin may be prepared according to the method described in Patents FR 2,294,697 and U.S. Pat. No. 4,024,175.

Detailed Description Text (29):
As pharmaceutically acceptable salts of riluzole and of gabapentin, there may be mentioned in particular the addition salts with inorganic acids such as hydrochloride, sulfate, nitrate, phosphate or organic acids such as acetate, propionate, succinate, oxalate, benzoate, fumarate, maleate, methanesulfonate, isethionate, theophilline acetate, salicylate, phenolphthalinate, methylene-bis-.beta.-oxynaphthoate or substitution derivatives of these derivatives.

Detailed Description Text (31):
The present invention also relates to the pharmaceutical compositions comprising the combination of riluzole and of gabapentin or one of their pharmaceutically acceptable salts, in the pure state or in the form of a combination with one or more compatible and pharmaceutically acceptable diluents and/or adjuvants and/or optionally in combination with another pharmaceutically compatible and physiologically active product.

Detailed Description Text (33):
As liquid compositions for oral administration, use may be made of pharmaceutically acceptable solutions, suspensions, emulsions, syrups and elixirs containing inert diluents such as water, ethanol, glycerol, vegetable oils or paraffin oil. These compositions may comprise substances other than the diluents, for example wetting products, sweeteners, thickeners, flavorings or stabilizers.

Detailed Description Text (36):
The present invention also relates to the use of the combination of riluzole and of gabapentin or one of their pharmaceutically acceptable salts for the preparation of a medicament useful for the prevention and/or treatment of motoneuron diseases and, in particular, amyotrophic lateral sclerosis, progressive spinal amyotrophy, infantile spinal amyotrophy or primary lateral sclerosis.

Detailed Description Text (37):
The present invention also relates to the method of preventing and/or of treating patients suffering from motoneuron diseases and, in particular, from amyotrophic lateral sclerosis, progressive spinal amyotrophy, infantile spinal amyotrophy or primary lateral sclerosis which consists in administering to the patient a combination of riluzole and of gabapentin or one of their pharmaceutically acceptable salts either simultaneously or separately or spaced out over time.

Detailed Description Text (38):
The doses depend on the desired effect, the duration of the treatment and the route of administration used; they are generally from 10 to 400 mg per day by the oral route for an adult with unit doses ranging from 10 to 200 mg of riluzole and from 100 to 2400 mg per day by the oral route for an adult with unit doses of 100 to 400 mg of gabapentin.

Detailed Description Paragraph Table (1):
ALS serum 0% 0.1% 0.1% 0.1% 0.1% Riluzole (M) 0 0 3 .times. 15.sup.-5 0 3 .times. 15.sup.-5 Gabapentin (M) 0 0 0 10.sup.-5 10.sup.-5 Number of 13 3 7 6 12 motoneurons (per 26 4 9 5 19 experiment and 19 0 4 5 18 per well 36 4 9 9 17 diameter) 33 2 11 2 18 33 4 7 9 14 25 5 6 1 23 32 2 7 3 21 Mean 27.1 3.0 7.5 5.0 17.8 (.+-. SEM) .+-.2.8 .+-.0.6 .+-.0.8* .+-.1.1* .+-.1.3** *p = 0.0003 **p < 00001

CLAIMS:

1. A pharmaceutical composition or kit, comprising, in combination, riluzole and gabapentin or a pharmaceutically acceptable salt thereof, in synergistically effective amounts to promote motoneuron survival.

2. The combination according to claim 1, in which said riluzole or salt thereof is present in an amount of 10 to 400 parts by weight per 300 to 2400 parts by weight of said gabapentin or salt thereof.

7. The combination of claim 1 in the form of a kit in which said riluzole or salt thereof is packaged separately from said gabapentin or salt thereof.

8. The combination of claim 1 in which said riluzole or salt thereof and said gabapentin or salt thereof are combined in a single pharmaceutically acceptable composition.

10. The method according to claim 4, in which the times of administration of the riluzole drug and of the gabapentin drug of said combination are spaced out over time.

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L19: Entry 1 of 2 File: USPT

DOCUMENT-IDENTIFIER: US 6395300 B1
TITLE: Porous drug matrices and methods of manufacture thereof

Abstract Text (1):
Drugs, especially low aqueous solubility drugs, are provided in a porous matrix form, preferably microparticles, which enhances dissolution of the drug in aqueous media. The drug matrices preferably are made using a process that includes (i) dissolving a drug, preferably a drug having low aqueous solubility, in a volatile solvent to form a drug solution, (ii) combining at least one pore forming agent with the drug solution to form an emulsion, suspension, or second solution, and (iii) removing the volatile solvent and pore forming agent from the emulsion, suspension, or second solution to yield the porous matrix of drug. The pore forming agent can be either a volatile liquid that is immiscible with the drug solvent or a volatile solid compound, preferably a volatile salt. In a preferred embodiment, spray drying is used to remove the solvents and the pore forming agent. The resulting porous matrix has a faster rate of dissolution following administration to a patient, as compared to non-porous matrix forms of the drug. In a preferred embodiment, microparticles of the porous drug matrix are reconstituted with an aqueous medium and administered parenterally, or processed using standard techniques into tablets or capsules for oral administration.

Detailed Description Text (53):
Examples of other drugs useful in the compositions and methods described herein include ceftriaxone, ketoconazole, ceftazidime, oxaprozin, albuterol, valacyclovir, urofollitropin, famciclovir, flutamide, enalapril, mefformin, itraconazole, buspirone, gabapentin, fosinopril, tramadol, acarbose, lorazepan, follitropin, glipizide, omeprazole, fluoxetine, lisinopril, tramsdol, levofloxacin, zafirlukast, interferon, growth hormone, interleukin, erythropoietin, granulocyte stimulating factor, nizatidine, bupropion, perindopril, erbumine, adenosine, alendronate, alprostadil, benazepril, betaxolol, bleomycin sulfate, dexfenfluramine, diltiazem, fentanyl, flecainid, gemcitabine, glatiramer acetate, granisetron, lamivudine, mangafodipir trisodium, mesalamine, metoprolol fumarate, metronidazole, miglitol, moexipril, monteleukast, octreotide acetate, olopatadine, paricalcitol, somatropin, sumatriptan succinate, tacrine, verapamil, nabumetone, trovafloxacin, dolasetron, zidovudine, finasteride, tobramycin, isradipine, tolcapone, enoxaparin, fluconazole, lansoprazole, terbinafine, pamidronate, didanosine, diclofenac, cisapride, venlafaxine, troglitazone, fluvastatin, losartan, imiglucerase, donepezil, olanzapine, valsartan, fexofenadine, calcitonin, and ipratropium bromide. These drugs are generally considered to be water soluble.

Detailed Description Text (76):
The choice of solvent depends on the drug. In a preferred embodiment, the solvent is an organic solvent that is volatile, has a relatively low boiling point, or can be removed under vacuum, and which is acceptable for administration to humans in trace amounts. Representative solvents include acetic acid, acetaldehyde dimethyl acetal, acetone, acetonitrile, chloroform, chlorofluorocarbons, dichloromethane, dipropyl ether, diisopropyl ether, N,N-dimethlyformamide (DMF), foramide, demethyl sulfoxide (DMSO), dioxane, ethanol, ethyl acetate, ethyl formate, ethyl vinyl ether, methyl ethyl ketone (MEK), glycerol, heptane, hexane, isopropanol, methanol, isopropanol, butanol, triethylamine, nitromethane, octane, pentane, tetrofuran (THF), toluene, 1,1,1-trichloroethane, 1,1,2-trichloroethylene, water, xlene, and combinations thereof. In general, the drug is dissolved in the volatile solvent to form a drug solution having a concentration of between 0.01 and 80% weight to volume (w/v), more

preferably between 0.025 and 30% (w/v).

Detailed Description Text (82):
The selection of liquid pore forming agents will depend on the drug solvent. Representative liquid pore forming agents include water; dichloromethane; alcohols such as ethanol, methanol, or isopropanol; acetone; ethyl acetate; ethyl formate; dimethylsulfoxide; acetonitrile; toluene; xylene; dimethylforamide; ethers such as THF, diethyl ether, or dioxane; triethylatnine; foramide; acetic acid; methyl ethyl ketone; pyridine; hexane; pentane; furan; water; and cyclohexane.

Detailed Description Text (138):
Production of a Porous Nifedipine Matrix Using Ammonium Bicarbonate as a Pore Forming Agent, PEG 3350 and TWEEN.TM. 80 as Wetting Agents, Polyvinylpyrrolidone as a Bulking Agent, and Ethanol as a Solvent

Detailed Description Text (139):
A nifedipine-loaded organic solution was prepared by dissolving 0.76 g of nifedipine, 0.28 g of PEG 3350, and 2.72 g of polyvinylpyrrolidone K-15 in 170 mL of ethanol. An aqueous solution composed of 1.62 g of ammonium bicarbonate and 3 mg of TWEEN.TM. 80 in 30 mL of DI water was added to the ethanol solution and mixed. The resulting solution was spray dried using process conditions of 20 mL/min solution flow rate, 100 kg/hr drying gas rate, and 36.degree. C. outlet temperature.

Detailed Description Text (141):
Production of a Porous Nifedipine Matrix Using Ammonium Bicarbonate as a Pore Forming Agent, PEG 3350 and PLURONIC.TM. F127 as Wetting Agents, Polyvinylpyrrolidone as a Bulking Agent, and Ethanol as a Solvent

Detailed Description Text (142):
A nifedipine-loaded organic solution was prepared by dissolving 0.76 g of nifedipine, 0.28 g of PEG 3350, and 2.72 g of polyvinylpyrrolidone K-15 in 170 mL of ethanol. An aqueous solution composed of 1.62 g of ammonium bicarbonate and 3 mg of PLURONIC.TM. F127 in 30 mL of DI water was added to the ethanol solution and mixed. The resulting solution was spray dried using process conditions of 20 mL/min solution flow rate, 100 kg/hr drying gas rate, and 36.degree. C. outlet temperature.

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L19: Entry 2 of 2 File: USPT

DOCUMENT-IDENTIFIER: US 6294198 B1
TITLE: Pharmaceutical tablet formulation containing gabapentin with improved physical and chemical characteristics and method of making the same

Abstract Text (1):
A pharmaceutical formulation form with improved physical and chemical characteristics, comprising gabapcntin in tablet form for oral administration. The tablet form can be prepared by spray-coating gabapentin with a binder solution and compressing the spray-coated gabapentin into non-friable, stable tablets. This method is particularly useful for tablet formulations that require large doses of active drug.

Brief Summary Text (3):
This invention is generally directed to pharmaceutical formulations with improved physical and chemical characteristics, comprising gabapentin in tablet form for oral administration. The tablet form can be prepared by spray-coating gabapentin with a binder solution and compressing the spray-coated gabapentin into non-friable, stable tablets. This invention is also generally directed to a method of producing pharmaceutical formulations in tablet form which contain large doses of active drug by spray-coating the active drug with a binder solution and compressing the spray-coated active drug into tablets.

Brief Summary Text (10):
IE 3089/90 issued to Augart, et. al., discloses a process for stabilizing pharmaceutical compositions containing gabapentin in solid form. The process entails hydrolyzing gabapentin with a semi-concentrated mineral acid and then converting gabapentin into a solid pharmaceutical composition containing hydroxypropyl methylcellulose, polyvinylpyrrolidine, crospovidone, maize starch, cyclodextrin, talcum, co-polymer of dimethylaminomethacrylic acid and/or neutral methacrylic acid ester.

Brief Summary Text (11):
Various patent applications and patents disclosing processes for preparing the gabapentin, and its methods of use are disclosed in PCT 98/28255, U.S. Pat. No. 4,024,175, U.S. Pat. No. 4,087,544, U.S. Pat. No. 5,084,479, U.S. Pat. No. 4,960,931, and U.S. Pat. No. 4,894,476.

Brief Summary Text (13):
It has been discovered that pharmaceutical formulations containing the active drug gabapentin can be produced with large doses of gabapentin but still be small enough for a patient to swallow. It has also been discovered that pharmaceutical formulations containing gabapentin in tablet form can be produced having improved characteristics such as hardness, friability and stability. It has further been discovered that the pharmaceutical formulations containing gabapentin can be produced in tablet form by spray-coating gabapentin particles with a binder solution and compressing the spray-coated particles into tablets. This method is also applicable to other pharmaceutical tablet formulations that require large doses of active drug for oral administration.

Brief Summary Text (14):
Thus, one aspect of the present invention is a pharmaceutical tablet comprising more than about 76% by weight of gabapentin. A second aspect of the invention is a

pharmaceutical tablet comprising more than about 76% by weight of gabapentin, a friability of less than about 1%, a hardness of about 10 kp to about 20 kp and a lactam level, a major degradation product of gabapentin, of less than about 0.4% by weight of the tablet composition.

Brief Summary Text (15):
A first preferred embodiment of the invention is that the pharmaceutical tablet comprises more than about 88% by weight of gabapentin. A second preferred embodiment is that the tablet has a friability of less than about 0.8%. A third preferred embodiment is that the tablet has a hardness of about 14 kp to about 16 kp. A fourth preferred embodiment of the invention is that the tablet has a lactam level of less than 0.2%.

Brief Summary Text (16):
An additional aspect of the invention is a pharmaceutical tablet comprising more than about 76% by weight of gabapentin, said tablet being formed from gabapentin particles spray-coated with a binder solution, mixed with a disintegrant and a lubricant, and then compressed into the tablet.

Brief Summary Text (19):
spray-coating the binder solution on gabapentin particles to achieve spray-coated gabapentin particles; and

Brief Summary Text (20):
compressing the spray-coated gabapentin particles into a tablet for oral administration to a patient, where the tablet contains more than 76% by weight of gabapentin.

Drawing Description Text (3):
FIGS. 2 and 3 show a plot of tablet hardness versus compression force for tablets containing, respectively, 600 mg and 800 mg of gabapentin made in accordance with Example 1.

Detailed Description Text (3):
According to the "Physician's Desk Reference.RTM.", 53.sup.rd Edition, Copyright 1999 Medical Economics Company, Inc., page 2302, gabapentin is used for adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. Gabapentin exists in a crystalline form and exhibits poor compressibility and compactibility. Compressibility is the ability of a powder to decrease in volume under pressure, while compactibility is the ability of a powder to be compressed into a tablet of a certain hardness or crushing strength. These detrimental characteristics of gabapentin cause capping and lamination defects during compression of gabapentin into tablets. A capping defect means that there is partial or complete separation of the top or the bottom crowns of a tablet from the main body. A lamination defect means that there is a separation of a tablet in two or more layers.

Detailed Description Text (4):
The conventional approach to remedying these tableting problems is to introduce excipients as compression aids. However, the inclusion of additional excipients can adversely affect the stability of gabapentin. Also, the more excipients used in a composition the more expensive and time-consuming commercial production becomes. Furthermore, an increase in the amount of excipients results in an increase in the tablet size. Large tablets are uncomfortable to swallow and result in low patient compliance.

Detailed Description Text (6):
The problem encountered with the inclusion of large amounts and/or number of excipients to a gabapentin formulation is that a number of excipients were not compatible with gabapentin and resulted in stability problems such as degradation. Gabapentin has been found to degrade into lactam, resulting in a decrease in the potency of gabapentin over time. Therefore, it is necessary to avoid degradation of gabapentin over the shelf life of the product. The shelf life of the product is generally two years from completion of manufacture. The level of degradation over the shelf life of the tablets can be determined by storing the product in closed

containers for a three-month period at 45.degree. C. and 75% relative humidity. Tablets containing gabapentin should have no more than about 0.4% by weight of lactam as determined by High Performance Liquid Chromatography (HPLC) at the end this three-month period. Preferably, gabapentin tablets should contain no more than about 0.2% by weight of lactam. By using methods such as HPLC or Thin Layer Chromatography for the analysis of degradation products, including lactam, one may determine the compatibility of excipients.

Detailed Description Text (7):
Another difficulty encountered in producing gabapentin tablets is that gabapentin is not amenable to traditional wet granulation techniques. Because the viscosity of the binder solution increases with an increase in the binder content, to apply a functional amount of binder for gabapentin, the amount of solvent has to be increased. This results in a wet granulation that is in a semi-liquid state and is not suitable for conventional drying methods. Therefore, the wet granulation technique has to be done in multiple stages where a portion of binder solution is added, followed by drying, then the next portion of binder solution and so forth. The wet granulation process is also conducted at elevated temperatures and accompanied by wetting gabapentin, which may be detrimental to the stability of gabapentin, cause polymorph conversion and change the crystalline structure of the active drug. This problem is eliminated by using a spray-coating method wherein a binder is dissolved in a solvent to form a binder solution which is then spray-coated on the drug particles. By using this method substantially all of the solvent is evaporated as it is applied, leaving a film of binder around the drug particles, and the process is conducted at or below room temperature.

Detailed Description Text (8):
In accordance with the present invention, spray-coating techniques are used to produce a compressible granulation containing gabapentin. Spray-coating gabapentin particles with a suitable binder solution produces a material that can be compressed into tablets having high hardness, low friability, and a size patients can swallow. Preferably, the pharmaceutical tablet comprises more than about 76% by weight of gabapentin. More preferably, the pharmaceutical tablet for commercial production comprises more than about 88% by weight of gabapentin. The tablets of the present invention can contain from about 500 mg to about 800 mg of gabapentin. More preferably the tablets will contain about 600 mg to 800 mg of gabapentin.

Detailed Description Text (10):
In the present invention any binder solution known to form a suitable spray solution can be used. For example, binders such as water-soluble derivatives of cellulose, gelatins, sugars, natural and synthetic gums, polyethylene glycol and combinations thereof, dissolved in a solvent such as ethanol, isopropyl alcohol, methanol, methylene chloride, acetone or combinations thereof, can by used. Preferably, the binder solution comprises hydroxypropyl cellulose dissolved in an alcohol, such as ethanol.

Detailed Description Text (11):
The solution may be prepared by any method that permits dissolution of binder to produce a homogenous solution, mixture or dispersion, such that formulations may be prepared that will contain a uniform amount of the binder. The concentration of binder in solution will depend upon the components used and the desired viscosity. For example, a binder solution can have up to 30% of povidone or copolyvidone. This binder solution is sprayed onto the gabapentin particles at a controlled temperature and airflow. Gabapentin is commercially available in a variety of particle size ranges such as about 10 .mu.m to about 250 .mu.m. Preferably the particle size range is about 25 .mu.m to about 75 .mu.m. Examples of suitable commercial spray-coating techniques are described, for example, in "Spray Drying Handbook", 4.sup.th ed., K. Masters, which is incorporated by reference.

Detailed Description Text (12):
A preferred method of spray-coating involves the use of fluid-bed processing equipment. Fluid-bed processing involves the use of air that passes up through the gabapentin particles and fluidizes them. The binder solution is applied to the particles through a pneumatically atomized nozzle equipped in the fluid-bed processing equipment. The solvent from the binder solution is concurrently removed from the

coated particles under controlled temperature and airflow conditions than can be obtained by routine experimentation. By maintaining the ratio of airflow to spray rate of binder solution, an isothermic process can be achieved. This allows the application of a large amount of binder solution in a one step process while eliminating excessive heat and moisture that can be detrimental to the stability of gabapentin.

Detailed Description Text (16):
For ease of swallowing, it may be desirable to coat the tablet containing gabapentin. Examples of acceptable commercial coating processes are described in "The Theory and Practice of Industrial Pharmacy, 3.sup.rd ed.", Lachman Lieberman, Kanig, pp. 359-373, which is incorporated by reference. Coating materials may include polymers such as hydroxypropyl methylcellulose, ethylcellulose, povidone, and polyethylene glycol; plasticizers such as castor oil, glycol and propylene glycol; and colorants such as dyes and lakes of dyes. Commercially available color coating systems such as Opadry.RTM. systems (Colorcon) may be also be used.

Detailed Description Text (19):
The tablet must be of sufficient crushing strength or hardness to withstand the coating process without chipping or breaking. The hardness of the tablets prepared in accordance with the present invention can be measured by known methods as described, for example, in, "The Theory and Practice of Industrial Pharmacy, 3.sup.rd ed.", Lachman Lieberman, Kanig, incorporated herein by reference. Hardness or crushing strength is the amount of force required to fracture the tablet. Typically a larger tablet requires a higher hardness to withstand the mechanical shocks of processing as well as subsequent consumer handling. However, the hardness should not be so high that it adversely effects disintegration and dissolution rates of the tablets. Preferably, the hardness of the gabapentin tablets is about 10 kp to about 20 kp. More preferably, the hardness of the gabapentin tablets is about 14 kp to about 15 kp.

Detailed Description Text (21):
The poor compactibility and compressibility properties of gabapentin are illustrated in FIG. 1 which is a plot of tablet hardness versus compression force for tablets made by: dry granulation (.tangle-solidup.), wet granulation (.circle-solid.), and the present invention (.diamond-solid.). The composition of the tablets is identical and differs only in the method of manufacture. The composition of the tablets comprise: 88.9% gabapentin, 3.5% hydroxypropyl cellulose, 5.8% crospovidone and, 1.8% calcium stearate (expressed as w/w of the tablet weight).

Detailed Description Text (22):
In the dry granulation process, gabapentin, hydroxypropyl cellulose, crospovidone, and calcium stearate were sieved through a 20 mesh sieve and blended together in a V-blender. The resulting blend was then slugged on a tablet press using 1/2 inch round flat-faced punches. The slugs were ground through an 18 mesh sieve using an oscillator and then compressed into tablets. This process produced tablets that had low hardness and a friability of 100% because every tablet exhibited breakage such as capping. As FIG. 1 demonstrates, the tablets produced by this method had a maximum hardness less than 3 kp.

Detailed Description Text (23):
In the wet granulation process, gabapentin was placed in a high shear mixer-granulator and mixed with a solution containing 10% hydroxypropyl cellulose in alcohol. The wet material was dried in a fluid-bed dryer and then milled through a comminuting mill equipped with a perforated plate with 0.0020" diameter holes. The milled material was placed back in the granulator and another portion of the hydroxypropyl cellulose solution was added while mixing. This wet material was again dried and mixed. This cycle was repeated until all of the binder solution was incorporated into the granulation. The milled granules were then blended with crospovidone and calcium stearate in a V-blender and compressed into tablets on a high speed, force fed tablet press. Tablets produced by the wet granulation process achieved a maximum hardness of only 11 kp and exhibited an unacceptable friability level of 2.0%. Furthermore, because of the multiple applications of binder solution and intermittent drying, the gabapentin particles were subjected to a large amount of moisture and heat which is detrimental to the stability of gabapentin.

Detailed Description Text (25):

The 600 mg tablets produced by the present invention achieved a desired hardness strength of 14 kp and a friability of 0.01%. As shown in FIG. 2, the 600 mg tablets made in accordance with Example 1 had a range of 10 kp to 22 kp. The 800 mg tablets produced by the present invention achieved a desired hardness strength of 16 kp and a friability of 0.04%. The hardness range of the 800 mg tablets made in accordance with Example 1 was 10 kp to 25 kp as show in FIG. 3. Furthermore, this one set spray-coat application of binder solution did not require excess excipients, moisture, or heat which can be detrimental to the stability of gabapentin.

Detailed Description Text (28):
Gabapentin tablets of the present invention are produced by applying a coating of binder solution comprising hydroxypropyl cellulose dissolved in alcohol, through a pneumatically atomized nozzle. The binder solution containing 7.5% hydroxypropyl cellulose is prepared by slowly adding hydroxypropyl cellulose, to alcohol and mixing the solution at room temperature for approximately 60 minutes or until the binder is uniformly dispersed and a clear homogenous solution is achieved.

Detailed Description Text (29):
Gabapentin, supplied by Teva Tech, Ltd (Israel) and having a particle size in the range of 10 .mu.m to 125 .mu.m, is loaded into the product container of a fluid-bed processor.

Detailed Description Text (37):
The process air volume is set to 100 cfm and gabapentin is fluidized. When the product temperature reaches about 25.degree. C. to about 28.degree. C., the binder solution is applied. This solution is introduced through a pneumatically atomized nozzle positioned in the expansion chamber of the fluid bed processor. The fluidized gabapentin particles are thus coated with the binder solution.

Detailed Description Text (40):
As used in the claims, gabapentin shall mean gabapentin itself, gabapentin analogs, all pharmaceutically acceptable salts of gabapentin, all pharmaceutically acceptable salts of gabapentin analogs, all combinations of pharmaceutically acceptable salts of gabapentin, all combinations of pharmaceutically acceptable gabapentin analogs, or all combinations of gabapentin itself with its pharmaceutically acceptable salts.

Detailed Description Paragraph Table (1):
TABLE 1 Composition of a 600 mg Gabapentin Tablet INGREDIENT AMOUNT PER TABLET Gabapentin 600 mg Hydroxypropyl Cellulose, NF 24 mg 75-150 cps (Klucel LF) Crospovisone (Polyplasdone XL) 39 mg Calcium Stearate 12 mg TOTAL WEIGHT 675 mg

Detailed Description Paragraph Table (2):
TABLE 1 Composition of a 600 mg Gabapentin Tablet INGREDIENT AMOUNT PER TABLET Gabapentin 600 mg Hydroxypropyl Cellulose, NF 24 mg 75-150 cps (Klucel LF) Crospovisone (Polyplasdone XL) 39 mg Calcium Stearate 12 mg TOTAL WEIGHT 675 mg

Detailed Description Paragraph Table (3):
TABLE 3 Composition of a 800 mg Gabapentin Tablet INGREDIENT AMOUNT PER TABLET Gabapentin 800 mg Copolyvidone 32 mg Crospovidone (Polyplasdone XL) 52 mg Calcium Stearate 16 mg TOTAL WEIGHT 900 mg

Other Reference Publication (1):
Product label for Neurontin.RTM. (Gabapentin Capsules and Gabapentin Tablets), revised Feb. 1999.

Other Reference Publication (2):
Product label for Neurontin.RTM. (Gabapentin) capsules, tablets and oral solution, FDA approved labeling text dated Oct. 12, 2000.

CLAIMS:

1. A pharmaceutical tablet comprising more than about 76% by weight of gabapentin, the tablet being formed from particles of gabapentin spray-coated with a binder solution, mixed with a disintegrant, and a lubricant, and then compressed into the tablet.

2. A pharmaceutical tablet of claim 1 comprising more than about 88% by weight of gabapentin.

4. A pharmaceutical tablet comprising more than about 88% by weight of gabapentin, the tablet being formed from particles of gabapentin spray-coated with hydroxypropyl cellulose dissolved in alcohol, mixed with crospovidone, and calcium stearate, and compressed into the tablet.

(b) spray-coating the binder solution on gabapentin particles to achieve a spray-coated gabapentin; and

(c) compressing the spray-coated gabapentin into a tablet for oral administration to a patient;

where the tablet contains more than about 76% by weight of gabapentin.

6. The method of claim 5 where the tablet contains more than about 88% by weight of gabapentin.

11. The method of claim 5 further comprising adding a disintegrant and a lubricant to the spray-coated gabapentin.

b) spray-coating the binder solution on gabapentin particles to produce spray-coated gabapentin;

c) mixing the spray-coated gabapentin with crospovidone and calcium stearate to obtain a final blend; and

where the tablet contains more than about 88% by weight of gabapentin.

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L22: Entry 4 of 17 File: USPT

DOCUMENT-IDENTIFIER: US 6319953 B1
TITLE: Treatment of depression and anxiety with fluoxetine and an NK-1 receptor antagonist

Detailed Description Text (28):
Suitable classes of anti-anxiety agent of use in the present invention include benzodiazepines and 5-HT.sub.1A agonists or antagonists, especially 5-HT.sub.1A partial agonists, and corticotropin releasing factor (CRF) antagonists. In addition to benzodiazepines, other suitable classes of anti-anxiety agent are nonbenzodiazepine sedative-hypnotic drugs such as zolpidem; mood-stabilizing drugs such as clobazam, gabapentin, lamotrigine, loreclezole, oxcarbamazepine, stiripentol and vigabatrin; and barbiturates.

Detailed Description Text (859):
For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

Detailed Description Text (943):
The active ingredients cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 50 mg, 100 mg and 300 mg of the CNS-penetrant NK-1 receptor antagonist per tablet.

Detailed Description Paragraph Table (3):
EXAMPLE 1 Tablets containing 50-300 mg of NK-1 antagonist and 5-10 mg of buspirone Amount mg NK-1 antagonist 50.0 50.0 100.0 100.0 300.0 300.0 buspirone 5.0 10.0 5.0 10.0 5.0 10.0 Microcrystalline cellulose 80.0 80.0 80.0 80.0 80.0 80.0 Modified food corn starch 80.0 80.0 80.0 80.0 80.0 80.0 Lactose 184.5 179.5 134.5 129.5 134.5 129.5 Magnesium Stearate 0.5 0.5 0.5 0.5 0.5 0.5

Detailed Description Paragraph Table (4):
EXAMPLE 1 Tablets containing 50-300 mg of NK-1 antagonist and 5-10 mg of buspirone

Amount mg NK-1 antagonist 50.0 50.0 100.0 100.0 300.0 300.0 buspirone 5.0 10.0 5.0 10.0 5.0 10.0 Microcrystalline cellulose 80.0 80.0 80.0 80.0 80.0 80.0 Modified food corn starch 80.0 80.0 80.0 80.0 80.0 80.0 Lactose 184.5 179.5 134.5 129.5 134.5 129.5 Magnesium Stearate 0.5 0.5 0.5 0.5 0.5 0.5